

Radioimmunotherapy in follicular lymphomas, a retrospective analysis of the Polish Lymphoma Research Group's (PLRG) experience

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Abstract

BACKGROUND: Ibritumomab is an ⁹⁰Yttrium (⁹⁰Y) labelled radioimmunoconjugate registered to treat follicular lymphoma relapsing or refractory after Rituximab therapy. Combining the specificity of anti CD20 monoclonal antibodies with the efficacy of radiotherapy, it is particularly effective in patients with advanced stages of disease with generalized lymphadenopathy.

MATERIAL AND METHODS: Twenty-one patients with follicular lymphoma, after failing 2–5 lines of previous treatment, were subjected to radioimmunotherapy in three Polish Lymphoma Research Group (PLRG) centres. Ibritumomab infusion was followed by 2 doses of Rituximab (250 mg/m² at day –7 and 0) to enhance its biodistribution. Radioimmuno-

conjugate was prepared in the Nuclear Medicine Departments of participating centres based on patient weight and full blood count results (14.8 MBq/kg, max 1200 MBq, reduced to 11.1 MBq/kg in cases with blood platelet 100 000–150 000 or leukocytes 1500–2000).

14.8 MBq/kg (0.4 mCi/kg)

100 thousand to 149 thousand/mm³ platelets

11.1 MBq/kg (0.3 mCi/kg)

RESULTS: The primary endpoint of the study was the assessment of response rate and haematological toxicity. Objective responses were observed in all patients, with 10 partial and 12 complete regressions. Cytopenia, starting 3–4 weeks after radioimmunotherapy, reflected haematological toxicity — the only important side effect. Thrombocytopenia was more pronounced, with platelet counts of < 50,000/ul in every second patient. One patient developed myelodysplastic syndrome 21 months after the procedure. After the medium time of follow up over 2 years, 2 patients died. Median progression free survival (secondary study endpoint) was 15 months.

CONCLUSIONS: Ibritumomab radioimmunotherapy is an efficient method of palliation treatment of heavily pre-treated follicular lymphoma patients, failing numerous previous treatment lines. Earlier application increases the number of complete responses and prolongs progression free survival.

Key words: radioimmunotherapy, ⁹⁰Y-ibritumomab tiuxetan (Zevalin), follicular lymphoma

Introduction

Zevalin (ibritumomab tiuxetan, IDEC-Y2B8) is a murine IgG1 kappa monoclonal antibody conjugated to tiuxetan (MXDTPA) that chelates yttrium or indium and is directed against the CD 20 molecules of B-lymphocytes. It was the first radioimmunoconjugate registered by the U.S. Food and Drug Administration (FDA) for lymphoma therapy, and the only one registered so far in Europe

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for follicular lymphoma (FL), refractory or relapsing after Rituximab. Our Polish experience in radioimmunotherapy (RIT) is based on over 60 patients treated by the Polish Lymphoma Research Group (PLRG) centres: 21 FL further described in this paper, 36 mantle cell lymphomas included in a PLRG MCL1 trial and 9 transformed lymphomas after autologous stem cell transplantation with a Zevalin containing conditioning regimen. During the last 3 years, a network of collaborating centres (nuclear medicine and haematology departments) has been developed to deal with the rather complicated logistics and to make the therapy method available to patients from all over the country.

Zevalin — mechanism of action

Radiolabelled monoclonal antibodies administered intravenously attach to CD20 (cluster differentiation), an antigen present on the surface of B-lymphocytes. In lymphoma patients, after a short distribution phase, most of the antibodies are bound in the tumour. Each of them is in fact a potent source of local radiotherapy damaging several adjacent cells and structures. In the tissues, the average penetration range of beta particles emitted by ^{90}Y is 5.3 mm; therefore, Zevalin is also effective in partly fibrosed, poorly vascularised lymph nodes. Even then, the best results are achieved if lymphoma infiltrates do not exceed 5–7 cm. RIT may be offered only to patients without substantial blood and bone marrow involvement (CD20 positive cells must be below 25%) to prevent irreversible stem cell damage. Circulating lymphoma cells and normal B-lymphocytes also bind to ibritumomab, altering its biodistribution and increasing toxicity of the procedure; therefore, their CD20 antigens have to be saturated by an unconjugated antibody, Rituximab, infused before radioimmunotherapy. Ibritumomab binds to lymphoma infiltrates all over the body, so its anti-tumour effect resembles total body irradiation (TBI) — one of the bone marrow transplant conditioning regimens. Ibritumomab biodistribution was confirmed by imaging studies performed while developing the protocol in the US, where the first of the two doses of antibody were labelled with a gamma emitter (indium-111). Biodistribution results were highly reproducible in typical cases (in a retrospective analysis, the treatment plan was changed in less than 2% of more than 900 patients [1]). Therefore, in Europe indium imaging is no longer regarded as necessary. Dosimetry is based only on patients' weight and results of a full blood count (FBC). Biodistribution may be altered in patients with a large tumour mass due to a "sink phenomenon" when most of the antibodies are bound i.e. in a massive splenomegaly. Although ibritumomab is a monoclonal antibody, its immunological mechanisms, like complement mediated cytotoxicity (CDC), play only a minor role as its dose is relatively small (nearly 400 times less than a standard dose of Rituximab). The effect of antibody mediated cellular toxicity (ADCC) is also moderate, as participating immunocompetent cells are likely to be killed in the first place. To summarize, ibritumomab RIT is a very clever way to deliver systemic radiotherapy, working best in patients with a disseminated nodal disease and without substantial bone marrow involvement.

Follicular lymphoma (FL)

Follicular lymphoma (FL) — a well-characterized disease entity — is the second most common form of non-Hodgkin's lymphoma

(NHL). Its frequency varies from over 30% of NHL in the US, through 15–25% in Western Europe to 5% in the Far East. A Polish Lymphoma Research Group (PLRG) epidemiologic survey, performed on 1060 NHL cases diagnosed in the Małopolska Region in the last 3 years [2], revealed unexpectedly low incidence of FL in Poland (5%). This unexpected trend was later confirmed in a national survey of over 5000 cases. Upon diagnosis, most patients are already in the advanced clinical stage, with at least some degree of bone marrow involvement. Other extranodal manifestations are rare. The clinical course of follicular lymphoma is variable: in most cases, the disease is indolent and slowly progressive, characterized by subsequent chemosensitive relapses. The average overall survival (OS) exceeds eight years, but there seems to be no plateau on the survival curve. At least 30% of patients are refractory to therapy, relapse early or transform to diffuse large B cell lymphoma (DLBCL).

Prognosis

Prognosis could be predicted by assessing simple clinical risk factors such as age (> 60 vs. < 60), Ann Arbor stage classification (III–IV vs. I–II), haemoglobin level (< 12 g/dL vs. > 12 g/dL), number of nodal areas involved (> 4 vs. < 4) and serum lactate dehydrogenase enzyme (LDH) level ($>$ normal vs. $<$ normal). Estimated ten-year survival is 70%, 50% and 35% for low, intermediate and high risk groups, respectively, defined as 0–1, 2 and 3 or more risk factors [3]. Although the Follicular Lymphoma International Prognostic Index (FLIPI) is an extremely simple and reproducible prognostic index, based on easily available clinical data, it does not indicate patients who will transform to DLBCL.

Follicular lymphoma treatment options

Treatment options of FL include: observation (wait and watch policy is still fully justified in elderly individuals with low dynamics of the disease), monotherapy with alkylating agents or purine nucleoside analogues, radiation therapy, combination chemotherapy, interferon, monoclonal antibodies and autologous or allogeneic stem cell transplantation. Introducing combination chemotherapy had a moderate, but yet existing, positive impact on OS [4], prolonging it from 84 to 93 months. In the past decade, several well-documented phase III studies (over 7000 patients randomized) have demonstrated further improvement in patients treated with the addition of interferon [5] and/or Rituximab [6, 7]. Chemo-immunotherapy with subsequent Rituximab maintenance is now considered the standard treatment of FL.

Material and methods

Radioimmunotherapy protocol and logistics

Since March 2004, 21 follicular lymphoma patients were treated with Ibritumomab in three PLRG centres in Cracow ($n = 17$), Wrocław ($n = 3$) and Warsaw ($n = 1$). Each radioimmunotherapy centre consists of Departments of Haematology/Oncology and Nuclear Medicine. Haematologists are responsible for patient qualification, treatment planning, financing the procedure, care during post ibritumomab cytopenias and later follow-up. The nuclear medicine departments are responsible for ^{90}Y ordering and handling, performing adequate dosimetry, final drug preparation and administration. For logistic reasons, the procedure is performed in Poland on Fridays, and the final qualification of patients

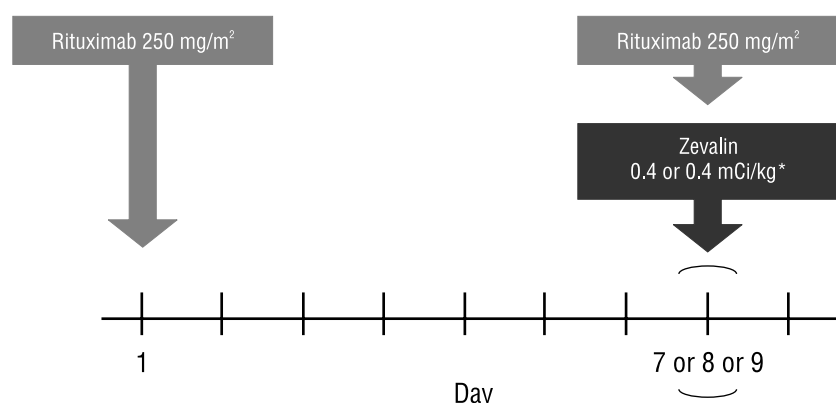


Figure 1. Zevalin treatment protocol in FL patients. *0.4 mCi (15 MBq)/kg when platelet count is $\geq 150,000/\text{mL}$; 0.3 mCi (11 MBq)/kg when platelet count is $100,000\text{--}150,000/\text{mL}$; the maximum dose is 1200 MBq (32 mCi).

had to be performed at least nine days earlier, to allow for the ordering, manufacture and transport of yttrium.

In our follicular lymphoma patients, Ibritumomab was given according to the standard protocol (Figure 1). Its infusion was preceded by two doses of Rituximab ($250 \text{ mg}/\text{m}^2$), seven days before and less than four hours before RIT. The final drug was prepared in the nuclear medicine departments from the commercially available ibritumomab “cool kit” — antibody and tiuxetan (yttrium chelator) manufactured by Bayer-Pharma-Schering (BSP), and ^{90}Y isotope sent from France (CIS bio International, Gif-sur-Yvette Cedex, France). The standard dose was $14.8 \text{ MBq}/\text{kg}$ (not exceeding the

maximum dose of 1200 MBq, which meant that each patient over 80 kg had an effective dose reduction). For patients with a mild thrombocytopenia ($100\text{--}150,000/\text{ul}$) or leucopenia ($1500\text{--}2000/\text{ul}$) protocol requires a dose reduction to $11.1 \text{ MBq}/\text{kg}$.

Demographics

The average age of FL patients subjected to radioimmunotherapy was 52 (38–67 range). There was a marked female predominance (14 out of 21). It was 2-6th line of therapy applied in cases of refractory or relapsing after a Rituximab containing regimen. Most of patients were heavily pre-treated; all were in ad-

Table 1. Earlier treatment and tumour burden of patients subjected to RIT

Diagnosis	Age	Earlier therapies	RIT — therapy line	Tumour burdens before RIT	Response to RIT
FL	55	6 × FC, 4 × CHOP, 4 × CHOP-R	4	5.0	PR
TFL	38	VACOP -B, 3 × CHOP-R, 3 × 2CdA-R + ESHAP + DICEP, IFRT	5	4.0	PR
MZL	56	6 × CHOP, 6 × CHOP, 4 × R, 1 × CHOP	4	8.0	PR
SLL	61	7 × COP, INF gamma, 4 × COP-R, 4 × CHOP-R, INF gamma-R	5	4.2	PR
FL	41	LP+1 × COP, 6 × CHOP, 6 × CHOP-R, CTX+ HDT (BEAM).	5	4.0	PR
MZL	53	6 × COP, 6 × CHOP-R, INFgamma-R	4	7.0	PR
FL	53	3 × COP, 4 × CHOP-R, 3 × FMD-R, IFRT	5	3.5	PR
FL	48	3 × CHOP, 3 × CC, INF+R, CTX-R	4	3.0	CR/CRu
FL	44	2 × COP+5 × FCM, 6 × CHOP, 8 × CHOP-Bleo, 2 × 2CdA+ 5 × F,	5	5.0	PR
FL	60	6 × CHOP, 6 × MEVA, 4 × R	4	4.0	CR/CRu
TFL	47	6 × CHOP, 4 × CC-R+ CTX-R	3	2.5	PR
FL	67	8 × CHOP, 4 × R, 4 × FCM-R	4	6.3	CR/CRu
FL		3 × CHOP, 3 × CC, 1 × ESHAP+CHOP-R	3	0.0	CR/CRu
FL	53	6 × COP, 3 × FC-R	3	4.4	CR/CRu
FL	65	Splenectomy	2	3.6	CR/CRu
FL	46	2 × LP, 6 × F-R, 5 × CHOP, 1 × DHAP+1 × CED+1 × VP+PBSCC	5	2.7	PR
FL	67	2 × CHOP, 4 × R, IFRT	4	1.4	CR/CRu
TFL	54	6 × CVP-R, 2 × CHOP-R + CHOP	3	3.5	PR
FL	44	6 × CVP-R	2	7.0	CR/CRu
FL	46	6 × CHOP, 6 × CVP-R	3	2.8	CR/CRu
FL	56	3 × CHOP, 4 × R, IFRT	4	1.7	CR/CRu

FL — follicular lymphoma; TFL — transformed follicular lymphoma; MZL — marginal zone lymphoma; SLL — small lymphocytic lymphoma; R — rituximab; FC — fludarabine, cyclophosphamide; CHOP — cyclophosphamide, vincristine, doxorubicin, prednisolone; 2 CdA — cladribine; ESHAP — etoposide, cytarabine, cisplatin, methylprednisolone; DICEP — cisplatin, cyclophosphamide, methylprednisolone; IFRT — involved field radiotherapy; COP — cyclophosphamide, vincristine, prednisolone; INF gamma — interferon gamma; LP — chlorambucil, prednisolone; HDT — high dose therapy; BEAM — carmustine, cytarabine, etoposide, melphalan; FMD — fludarabine, mitoxantrone, dexamethasone; CC — cyclophosphamide, cladribine; CTX — cyclophosphamide; FCM — fludarabine, cyclophosphamide, mitoxantrone; CHOP-Bleo — cyclophosphamide, vincristine, doxorubicin, prednisolone, bleomycin; F — fludarabine; MEVA — mitoxantrone, etoposide, vincristine, cytarabine; FC — fludarabine, cyclophosphamide; CED — cyclophosphamide, etoposide, dexamethasone; VP — etoposide, prednisolone; PBSCC — peripheral blood stem cell collection

vanced clinical stage with a measurable tumour burden at the time of RIT. Chemotherapy details are summarized in Table 1. The first nine patients were part of a "pre registration study" in which Bayer Schering Pharma (BSP) sponsored the drug for any patients fulfilling the registration criteria. Although a histopathological review performed later revealed two cases of marginal zone lymphoma (MZL) and one case of small lymphocytic lymphoma (SLL), we decided to include these patients in the survival analysis. In addition — somehow arbitrary — we included three patients with FL after transformation, where ibritumomab was used in a consolidation strategy.

Response criteria

Most patients had a later follow-up in one of the local centres; therefore, the response assessment varied. For the purpose of this analysis, we defined partial response (PR) as any measurable mass visible on imaging studies or bone marrow involvement seen in aspiration biopsy cytology. As a proper differentiation of complete response (CR) from complete response unconfirmed (CRu) is not possible without a thorough flow cytometry, cytogenetics and molecular analysis, we decided to place all other cases in the CR/CRu category.

Statistical analysis

Statistical analysis was based on the data gathered in March 2006. Both descriptive statistics, plotting Kaplan Meier curves of progression free and overall survival (PFS, OS) were performed using Statistica 6 software. A Cox-Mantel test was used to compare the survival curves in sub-group analysis.

Results

Ibritumomab was administered to 21 patients without any major protocol violations: 17 received 14.8 MBq/kg; in a further four cases the dose was reduced to 11.1 MBq/kg due to pretreatment mild thrombocytopenia (100–150 000/ul) or leucopenia (1500–2000/ul). Most of the patients experienced some degree of haematological toxicity: according to WHO grade III and IV, leucopenia (< 1500 WBC/ul) or thrombocytopenia (< 99 000/ul) was observed in 13/21 patients. The onset of cytopenia was postponed and occurred 3–6 weeks (average 4.5) after ibritumomab administration, which is characteristic for radioimmunotherapy, reflecting its effect on the STEM cells. Leucopenia lasted 0–15 weeks (2.9 on average): in five patients it was necessary to use growth factor granulocyte colony stimulating factor (G-CSF), but none of them developed serious infections that required treatment in a hospital (three upper respiratory tract infections were managed on outpatient basis). Thrombocytopenia was more pronounced (3.7 weeks, range 0–12), and although platelet transfusions were necessary only in three patients, most of them had to limit their normal activity during that period. Full blood count (FBC) results of 12 patients, whose RIT and the complete follow-up was performed at Cracow, are shown in Figure 2. In the first patient, handling ibritumomab before adequate plastic syringe shields were introduced caused local radiation related skin burns. During the follow-up, one case of myelodysplastic syndrome was reported 21 months after radioimmunotherapy: a rare side effect described in 1.5–2 % of patients 2–10 years after RIT [8].

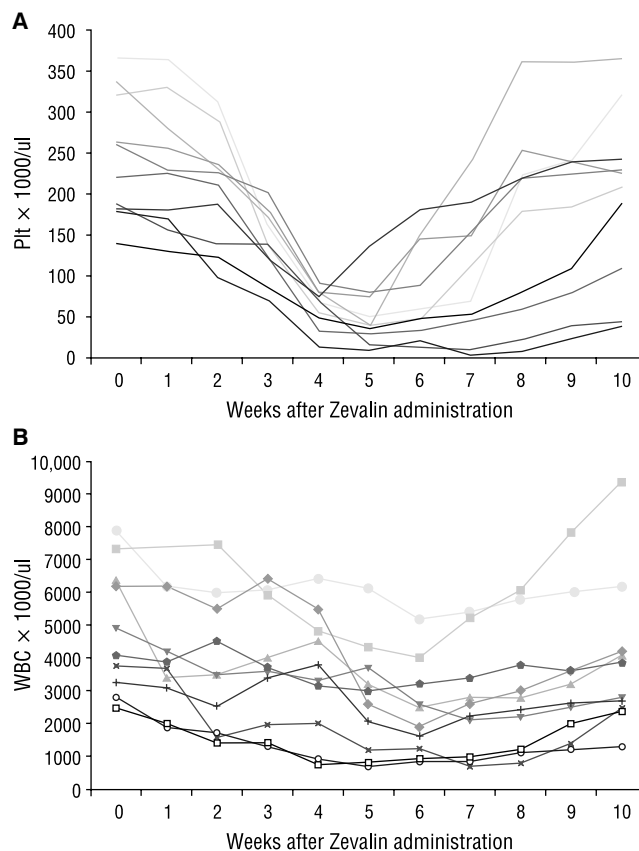


Figure 2. Blood platelet (Plt) (A) and white blood cell (WBC) (B) recovery, during cytopenia after Zevalin radioimmunotherapy.

All patients demonstrated an objective response to radioimmunotherapy (10 CR/CRu and 11 PR) lasting longer than responses after the previous therapy in 17 out of 21 cases. Four patients with a shorter time to progression were earlier subjected to an intensive therapy protocols (Zevalin — Carmustine, Cytarabine, Etoposide, Melphalan Z-BEAM transplant, 3 cycles of II line intensive chemotherapy or chemotherapy Cyclophosphamide, Doxorubicin, Vincristine, Prednisolon-Rituximab CHOP-R). Progression free survival (PFS) and OS (overall survival) are demonstrated on Kaplan Meier curves (Figure 3). The medium PFS of 15.8 months exceeds the average 12.9 months described in the literature [9], and median OS was still not reached after 45 months of follow-up.

Patients treated earlier in the course of the disease (2nd–3rd versus 4th–5th therapy line) had longer progression free survival (median PFS not yet reached, versus 15.4 months, Cox-Mantel test: $I = 2.068125$ $U = -3.34494$, $p = 0.02$). With only 21 patients included in the study, the influence of tumour mass before therapy and response to treatment (PR vs. CR/CRu) was not statistically significant.

The whole radioimmunotherapy procedure consisted of two outpatient visits, which allowed it to be offered to patients from all over the country. The expected haematological toxicity was fully manageable, although regular follow-up in local haematological departments with full blood count (FBC) analysis was necessary. For the first two months, until platelet recovery, the patients were advised not to work. Practically, the only costs were drug-related

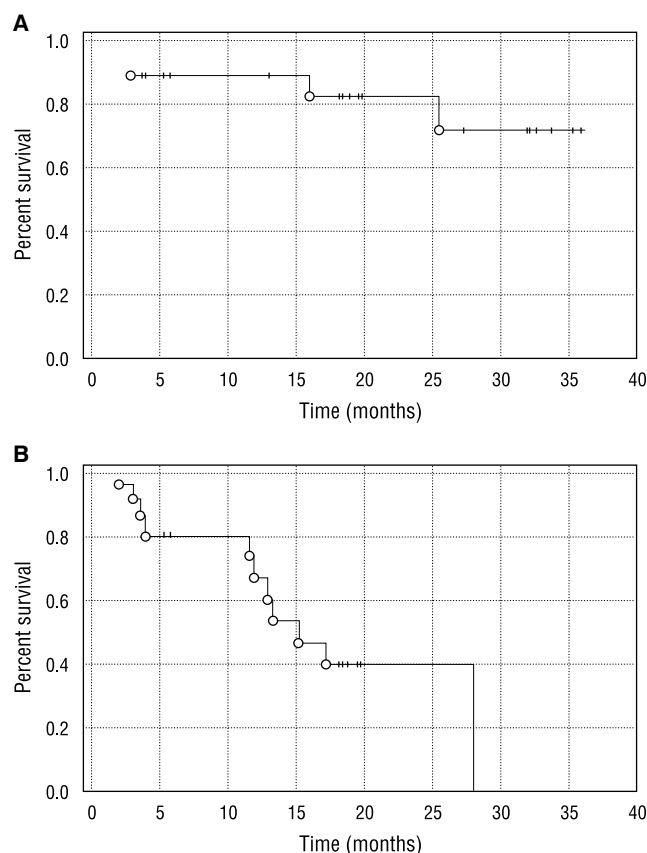


Figure 3. Overall survival (OS) (A) and progression free survival (PFS) (B) Kaplan Meier curves of FL patients after RIT.

(Ibritumomab itself, Ytracis and Rituximab), exceeding 18 700 Euro, which is comparable to the current standard: 2 years of Rituximab maintenance therapy.

Discussion

The Polish Lymphoma Research Group (PLRG) results of radioimmunotherapy in follicular lymphoma patients are fully comparable to those previously described in literature. Haematological toxicity was moderate and manageable. Treatment related myelodysplastic syndrome is an important warning, although our sample is too small to assess its incidence [8].

In Poland, Rituximab has not been registered for follicular lymphoma at diagnosis; therefore, the majority of our patients received sub-optimal first line therapy. Postponing chemoimmunotherapy until the disease relapsed or until it became refractory further postponed radioimmunotherapy. Progression free survival exceeding 15 months is three months longer than in the US registration trials [9, 10]; medium overall survival (OS) is still not reached after 45 months of observation. This may be explained by excluding patients with a very large tumour burden, where RIT is less effective. The largest measurable lymph nodes before treatment were 1.4–8 cm (average 4.0 cm) in diameter, and we could not, therefore, demonstrate a clear correlation between the tumour size and the treatment effectiveness (Figure 4). Although ibritumomab was given to most of our patients in the third and further treatment lines, the better outcome of those treated earlier was statistically signi-

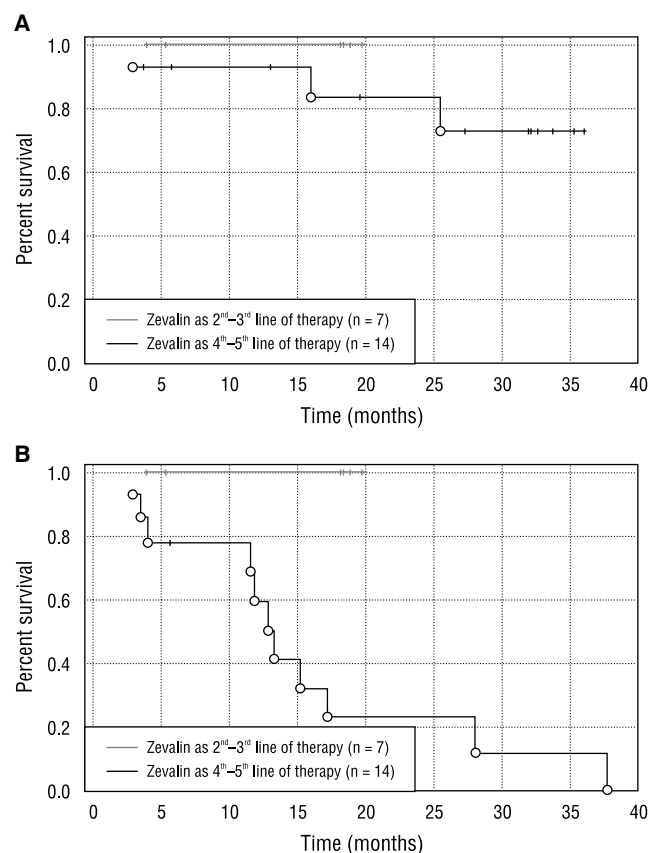


Figure 4. Overall survival (OS) (A) and progression free survival (PFS) (B) Kaplan Meier curves of FL patients after RIT. Subgroup analysis — impact of the number of therapy lines before RIT.

ficant (Figure 5). In our data there was no difference between the outcome of patients achieving complete or partial regression, but the patient numbers were low and the CR/CRu category was not well defined (Figure 6).

Which patients can merit the most from radioimmunotherapy? Ibritumomab maybe be used in FL algorithms in two different therapy strategies (Table 2). In the first “cure” is the ultimate, although perhaps unrealistic, target. This optimism is based on long lasting progression free survival (PFS) (sometimes more than 7 years) demonstrated in US registration studies [11]. The medium PFS increases with the quality of response: it ranges from 12 months in responders, to 23 months in CR/CRu and even 66 months in “true CR” patients [9, 12]. About 20% of responders and even 40% of those who remained in CR a year after the ibritumomab have a plateau on survival curves [13]. Clinical trials with Tositumomab (a monoclonal antibody conjugated with ¹³¹Iodine) led to similar conclusions. The long lasting responses were achieved in 20% of responders, and 40% of CR confirmed by a Masked Independent Randomized Radiology and Oncology Review (MIRROR) panel [14]. Being consequent with this approach, if all PR patients will eventually relapse, one should do everything possible to increase the CR rate. This could be achieved either by applying radioimmunotherapy earlier, before the disease becomes resistant to therapy, or by using ibritumomab as a consolidation strategy, after reducing the tumour burden by chemotherapy. The efficiency of the first approach was demonstrated by Emmanoul-

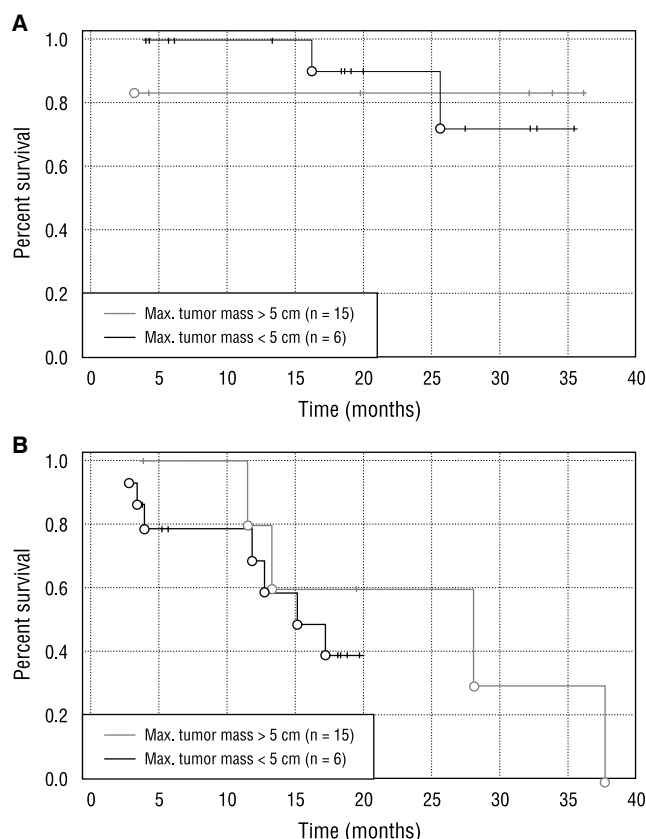


Figure 5. Overall survival (OS) (A) and progression free survival (PFS) (B) Kaplan Meier curves of FL patients after RIT. Subgroup analysis — impact of tumour size before RIT.

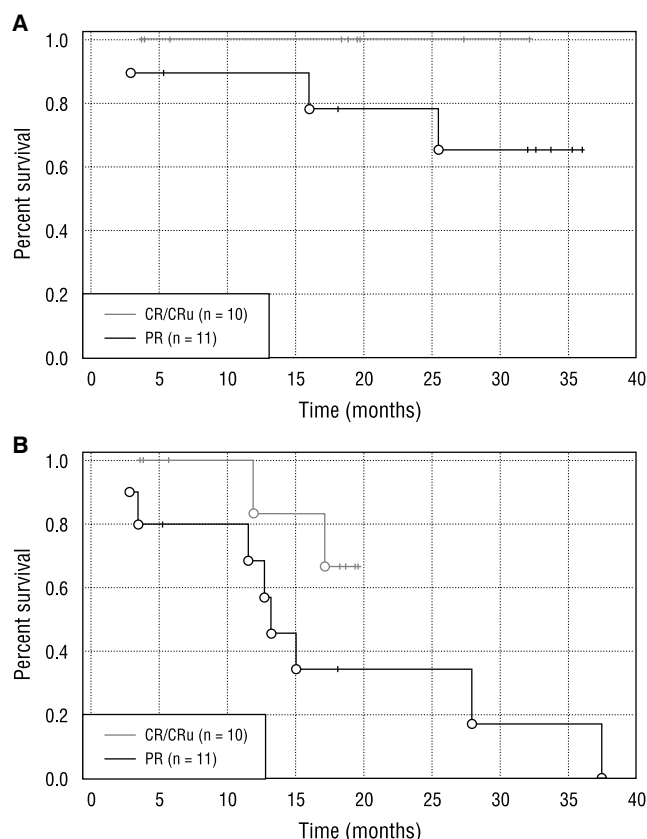


Figure 6. Overall survival (OS) (A) and progression free survival (PFS) (B) Kaplan Meier curves of FL patients after RIT. Subgroup analysis — impact of response to RIT.

ides [15]. Complete regression could be achieved in 62% of patients treated with ibritumomab at diagnosis, 54% of those in a first relapse, 40% after the previous 2 lines of therapy and less than 15% of those treated later. In one of the tositumomab studies [16], RIT was a consolidation after abbreviated first line CHOP chemotherapy. Complete regressions were achieved in 57/76 patients, and 40 were still in an on-going CR 3.5–7 years later (5 year progression free survival (PFS) and overall survival (OS) were 67% and 87% respectively). Consolidation radioimmunotherapy cannot be recommended as first line treatment in follicular lymphoma outside clinical trials because of the very good results of the present standard Cyclophosphamide, Vincristine, Prednisolone-Rituximab (CVP-R) or Cyclophosphamide, Doxorubicin, Vincristine, Prednisolone-Rituximab (CHOP-R) chemioimmunotherapy and the uncertainty of long-lasting adverse effects of RIT. Haematological toxicity depends on the direct effect on the stem cells [17]. Although it is possible to treat relapses after radioimmuno-

therapy with subsequent chemotherapy regimens [18], and even mobilize the stem cells for transplant purposes, more controlled studies with upfront radioimmunotherapy are necessary to fully address this issue.

The second place of ibritumomab in follicular lymphoma is in optimal palliation therapy for patients failing several other treatment modalities. In these heavily pretreated patients, the safety of the procedure and the quality of life (QoL) are most important. Disseminated disease, even when refractory to chemotherapy may still respond to radioimmunotherapy. Although complete remissions are rare (< 15% of the patients), the response rate is usually high (over 70%) [15] and the progression free survival exceeds that achieved after the preceding chemotherapy. Radioimmunotherapy is most effective in patients with tumours not exceeding 5–7 cm in size [19].

Ibritumomab radioimmunotherapy is a safe and feasible outpatient procedure. In typical cases it does not require dosimetry

Table 2. Possible place of Zevalin in FL therapy algorithm

Intend to "cure"	The best "palliation" possible	
Relatively early in the course of the disease (consolidation of 2nd line therapy?)	When?	In patients failing several therapy lines
Usually as consolidation strategy	How?	Usually monotherapy
High CR rate and long PFS	Main goal?	High RR for symptom relief, good QoL and minimal side effects

and haematological toxicity may be best predicted by FBC before the treatment (Figure 2). Although it usually requires from the patient a change in their lifestyle for 2–3 months after the therapy, it is an interesting alternative to two year long Rituximab maintenance. In FL, outside controlled clinical trials, we would suggest considering it relatively early in high risk cases (i.e. a PR after CVP-R or CHOP-R chemoimmunotherapy) and leaving it for until later relapses if the risk is low.

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